I. TERPENE SYNTHESES IN THE CARVONE SERIES

II. ATTEMPTED ACID-CATALYZED CYCLIZATIONS OF PHTHALIDES

BY

HENRY KINGSTON HALL, JR.

B.S., Polytechnic Institute of Brooklyn, 1944
M.S., Pennsylvania State College, 1946

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
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I. TERPENE SYNTHESES IN THE CARVONE SERIES

Substituted cyclohexenones are among the most important of the monocyclic terpenes. It was of interest to devise a new synthetic method which would give access to certain of these compounds hitherto not easily prepared. The transformation of cyclic 1,3-diketones to cyclohexenones seemed inviting.

An application of this procedure was undertaken for the synthesis of carvotanacetone (5-isopropyl-2-methyl-2-cyclohexenone). This compound is a naturally occuring terpene and also possesses the characteristic odor of dill and caraway oil, which owe their flavor to the structurally similar carvone. Several homologs of carvotanacetone have been synthesized in the same manner to relate their structure and odors.

5-Isopropylcyclohexane-1,3-dione was prepared from isobutylideneacetone and malonic ester by an improved procedure.

The conversion of this and similar 1,3-diketones was the subject of much experimentation. The change was finally realized by converting the diketone to the corresponding 3-chloro-2-cyclohexenone by the use of phosphorus trichloride. This halide was dehalogenated by stirring with zinc in a methanol solution of potassium iodide.

Another means of accomplishing the same transformation involved etherifying the enolic hydroxyl group, by an improved method, to form the corresponding 3-ethoxy-2-cyclohexenone. On treatment with one equivalent of lithium aluminum hydride this compound readily underwent replacement of the ethoxyl group by hydrogen. 5-Isopropyl-2-cyclohexenone was prepared in this way.

In the preparation of carvotanacetone and its 2-alkyl homologs, a methyl group could be introduced at the 2-position of the cyclohexenone by methylation of the diketone. By this reaction, followed by treatment with phosphorus trichloride and zinc, carvotanacetone was conveniently obtained.

Attempts to introduce an ethyl or β-chloroethyl group similarly resulted only in O-alkylation of the diketone. An alternate synthetic route to 2-ethyl-5-isopropylcyclohexane-1,3-dione was proposed. Ethyl *n*-butyroacetate was prepared from malonic ester and was condensed with isobutyraldehyde. It was hoped that the resulting ethyl isobutylidene-*n*-butyroacetate could be made to undergo a Michael condensation with malonic ester or tricarbethoxymethane, but these experiments were not successful.

Introduction of alkyl groups at the 3-position of the cyclohexenone was effected by the reaction of Grignard reagents with either the 1,3-diketones or the 3-ethoxy-2-cyclohexenones. The yields were small and it was necessary to isolate the ketones through the semicarbazones. In this manner 5-isopropyl-3-methyl-2-cyclohexenone, 3-ethyl-5-isopropyl-2-cyclohexenone, and 2,3-dimethyl-5-isopropyl-2-cyclohexenone were prepared.

The odors of these compounds were found to resemble that of carvotanacetone to a varying degree. In order of decreasing similarity they were 2,3-dimethyl-5-isopropyl-2-cyclohexenone, 3-ethyl-5-isopropyl-2-cyclohexenone, 5-isopropyl-3-methyl-2-cyclohexenone, and 5-isopropyl-2-cyclohexenone.

II. ATTEMPTED ACID-CATALYZED CYCLIZATIONS OF PHTHALIDES

A number of cases have been recorded in which lactones have been transformed to cyclopentenones by the action of acidic reagents. If phthalides, which structurally resemble lactones, could be caused to undergo a similar cyclization, this reaction would constitute a useful synthetic method for substituted indones.

Hydrogenation of 3-propylidenephthalide, obtained by the

reaction of butyric anhydride with phthalic anhydride, gave 3-propylphthalide. Distillation of this compound from phosphorus pentoxide at varying temperatures gave only tars.

3-Benzylphthalide was prepared by hydrogenation of 3-benzalphthalide. It could not be cyclized.

3-Phenylphthalide, prepared by reduction of *o*-benzoylbenzoic acid, was not cyclized on treatment with sulfuric acid or zinc chloride.

It was thought that the reaction of the pseudo-forms of γ- and δ-ketoacid chlorides with organic cadmium compounds might offer a new synthesis of lactones and phthalides. The reaction of *o*-benzoylbenzoyl chloride with diphenylcadmium was found to give unsatisfactory results. Treatment of levulinyl chloride with di-*n*-hexylcadmium gave a fair yield of impure lactone. This synthesis was not pursued further.

Several attempts to cyclize 3,3-disubstituted phthalides were also made. 3,3-Dibenzylphthalide was made by an improved procedure, consisting of the reaction of phthalide with benzylmagnesium chloride, followed by oxidation of the resulting methylol derivative.

Neither 3,3-dibenzylphthailde nor 3,3-diphenylphthalide underwent ring closure on treatment with sulfuric acid or zinc chloride.

VITA

The author was born in New York City on December 7, 1924. He attended public school, junior high school, and high school in that city. He attended the Polytechnic Institute of Brooklyn from September, 1941, to June, 1944, receiving his B.S. in that month. From October, 1944, to June, 1946, he attended the Pennsylvania State College and obtained his M.S. He has been enrolled at the University of Illinois since June, 1946.

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